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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/894,246	05/22/1998	MICHEL PERRICAUDET	EX95001-US	8790

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WILEY, REIN & FIELDING, LLP
ATTN: PATENT ADMINISTRATION
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 08/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/894,246	Applicant(s) PERRICAUDET ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 7-1-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/894,246 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' amendment filed 7-1-02 has been entered. Claims 26-64 have been canceled. Claims 65-108 have been added. Claims 65-108 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 66, 67, 85 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "selected from...and a monoclonal or a polyclonal antibody" in claims 66 and 85 is vague and renders the claims indefinite. It is unclear whether the group to be selected from comprises a monoclonal antibody or a polyclonal antibody or both. Claims 67 and 86 depend on claims 66 and 85, respectively, but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 82, 88 and 107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 82, 88 and 107 read on a recombinant adenovirus comprising a recombinant DNA containing a sequence coding for an adenoviral gp19k protein that contains one or more point mutations compared to wild type human Ad5 adenovirus sequence, and the gp19k protein retains an immunosuppressive activity.

The phrase "a sequence coding for an adenoviral gp19k protein that contains one or more point mutations compared to wild type human Ad5 adenovirus sequence, and the gp19k protein retains an immunosuppressive activity" is considered a new matter. The specification only discloses the immunosuppressive activity of gp19k protein in combination with a immunosuppressive agent, such as anti-CD4 antibody. Applicants' amendment filed 7-1-02 indicates that the specification describes site-directed mutagenesis (page 31, line 28 through page 32, line 4) and techniques for isolating homologue of gp19k (page 18, lines 15-20). The specification only discloses site-directed mutagenesis in general but fails to provide sufficient description for a sequence that contains one or more point mutations compared to a wild type human Ad5 sequence and encodes a mutated gp19k protein having immunosuppressive activity

as wild type gp19k protein or how to use the site-directed mutagenesis method to obtain said sequence encoding mutated gp19k protein that still retain immunosuppressive activity. The specification also fails to disclose the structural feature that contributes to immunosuppressive activity of gp19k protein and which amino acid residue(s) can be removed but the resulting mutated protein still retain the immunosuppressive activity of gp19k protein. Further, the disclosure of techniques, such as screening libraries, for isolating homologue of gp19k is irrelevant to introducing one or more point mutations to the sequence encoding wild type gp19k protein and the resulting mutated protein still retain the immunosuppressive activity of gp19k protein. Thus, the specification fails to provide support for "a sequence coding for an adenoviral gp19k protein that contains one or more point mutations compared to wild type human Ad5 adenovirus sequence, and the gp19k protein retains an immunosuppressive activity" that is considered a new matter.

6. Claims 102-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 102-108 are directed to a method of prolonging the survival of a cell expressing a sequence of interest comprising introducing a recombinant adenovirus to a cell of an animal, wherein the adenovirus contains the sequence of interest and a sequence encoding for an

adenoviral gp19k protein and **the expression of the sequence of interest results in prolonged cell survival *in vitro* or *in vivo*.** Claim 103 specifies the sequence of interest encodes a protein, ribozyme, or antisense RNA. Claim 105 specifies the sequence of interest encodes p53, aFGF, bFGF, factor VII, or factor IX.

The specification of the present application only discloses decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, and decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K.

The claims encompass any sequence of interest that encodes any protein, ribozyme and any antisense RNA. The specification fails to provide adequate guidance and evidence that expression of any of the sequence of interest encoding any protein, such as p53, aFGF, bFGF, factor VII, or factor IX, any ribozyme, or antisense RNA could result in prolonged cell survival *in vitro* or *in vivo*. It was known in the art that different proteins have different biological functions. Ribozyme, antisense RNA and protein contain different chemical structures, physical properties and biological functions. There is no evidence of record that any protein, ribozyme, or any antisense RNA could result in prolonged cell survival *in vitro* or *in vivo* except the disclosed gp19k protein in the present application. It was also well known in the art protein function is unpredictable from mere amino acid sequence and requires trial and error experimentation.

Thus, one skilled in the art at the time of the invention would not know how to use the claimed sequence of interest to prolong cell survival *in vitro* or *in vivo*, and would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 65-81, 83-87 and 89-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leibowitz et al., 1994 (N) in view of Linsley et al., 1992 (U) and Nabel et al., 1994 (Annals New York Academy of Sciences, Vol. 714, p. 247-252).

Claims 65-81, 83-87 and 89-101 are directed to a composition comprising an immunosuppressive agent (e.g. CTLA4Ig) and a recombinant adenovirus comprising a first recombinant DNA and a second recombinant DNA, wherein the second recombinant DNA contains a sequence encoding adenoviral gp19k protein and a method for expressing a sequence of interest from an adenovirus comprising consecutively or simultaneously administering to a subject an immunosuppressive agent and a recombinant adenovirus expressing the sequence of interest and the adenoviral gp19k protein. Claims 68-70 and 89-91 specify the first recombinant DNA encodes a protein, a ribozyme or an antisense RNA. Claims 71-79 and 92-94 specify the first and second recombinant DNAs constitute a single transcription entity, use same promoter, inserted in the same orientation, or inserted into different sites in the adenovirus genome. Claims 95-97 specify the immunosuppressive agent is administered both before and after administration of the adenovirus or administered simultaneously, and the adenovirus is administered by injection. Claims 98-101 specify the first recombinant DNA encodes a p53, aFGF, or bFGF etc.

Leibowitz teaches construction of a recombinant Ad5 adenovrius vector containing adenoviral E19 (i.e. gp19K) coding sequence operably linked to a promoter and infection of a wide variety of donor cells with said adenovirus vector to alter the presentation of MHC class I cell surface antigen on these cells and thereby allow introduction of these cells into a recipient

organism while reducing transplant rejection by the recipient organism's immune system (e.g. abstract, p. 9, 10). Leibowitz also teaches a method of effecting gene therapy in a recipient organism by transplanting into said recipient organism cells expressing a gene product of interest for an abnormal genetic condition and said transplanted cells have been treated with E19pk protein to alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system (e.g. p. 35).

Leibowitz does not teach combination of an immunosuppressive agent, such as CTLA4Ig, and a recombinant adenovirus vector expressing a sequence of interest and an adenovirus gp19k protein in a composition or for a method of expressing the sequence of interest by using said composition.

Linsley shows CTLA4Ig treatment *in vivo* suppresses T-cell dependent antibody responses to sheep erythrocytes, large doses of CTLA4Ig suppresses response to a second immunization (see e.g. abstract).

Nabel teaches using recombinant adenoviral vector expressing FGF-1 for gene transfer into vascular cells and discloses the problem of host immune response to the adenoviral vector for gene transfer (e.g. p. 248, 249).

It would have been obvious for one of ordinary skill at the time of the invention to combine the immunosuppressive agent with an adenovirus vector containing a sequence of interest and coding sequence for gp19k protein in a composition and the use of said composition for expressing the sequence of interest because immunosuppressive agent such as CTLA4Ig can

suppress T-cell dependent antibody response and E19pk protein can alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism's immune system and combining said agent and adenovirus vector would enhance their immunosuppressive effects. The arrangement of the sequence of interest and E19 gene in a vector, e.g. in a single transcriptional entity or in the same orientation, and the sequential order of administering immunosuppressive agent and adenovirus are routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill at the time the invention was made would have been motivated to generate a composition comprising an immunosuppressive agent such as CTLA4Ig and an adenoviral vector containing a sequence of interest and coding sequence for gp19k protein and the use of said composition for expressing the sequence of interest in order to reduce transplant rejection by the recipient organism's immune system by altering the presentation of MHC class I cell surface antigen on donor cells or to effect gene therapy in a recipient organism as taught by Leibowitz and suppresses T-cell dependent antibody responses as taught by Linsley with reasonable expectation of success. Further, the immune response triggered by adenovirus vector as taught by Nabel would also motivate one ordinary skill to combined the immunosuppressive agent and the adenoviral vector set forth above in order to suppress the host immune response while using adenoviral vector for gene transfer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.